



## REMARKS

### 1-Requirement for Restriction

The examiner required restriction to one of several groups of targets recited in the claims under 35 USC 1.121. The applicant has selected the receptor targets, as described above.

### 2- Amendment

### THE CLAIMS

Claims 1-91 are pending in this application, and no claims have been amended. Consideration and allowance of these claims is requested.

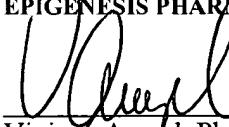
### THE SPECIFICATION

The applicant submitted with the Amendment of September 28, 2001, marked-up and clean copies of the amended specification pages. Further copies are enclosed herewith for the examiner's convenience. The amendments to the specification are fully supported by the specification, as filed and by the original claims. No objectionable new matter is believed to have been introduced by this amendment.

### THE FEE

The Assistant Commissioner, however, is hereby authorized to charge to PTO Account No. 50-1728, the amount of \$200.- for an extension fee of two months, which is herewith being requested. In view of the above amendments and remarks, this application is believed to be in condition for examination and allowance. Early notice to that effect is hereby solicited.

Respectfully submitted.  
EPIGENESIS PHARMACEUTICALS, INC.

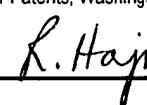
  
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January 4, 2002

\_\_\_\_\_  
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I hereby certify that this correspondence is being deposited at the United States Postal Service, First Class Mail in an envelope addressed to the Assistant Commissioner for Patents, Washington D C 20231, on January 4, 2002, by Rashida Haji.

  
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SIGNATURE

**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

**In the specification**

Section beginning from page 296, line 56, to page 298, line 60, has been amended as follows (from next page):



5           GGATATAGGT TTCCAATTAA GTACATGGTC AAGTATTAAC AGCACAAAGTG GTAGGTTAAC ATTAGAATAG  
 GAATTGGGTG TGGGGGGGGG GTTGCAGAGA ATATTTTATT TTAATTTTT GGATGAAATT TTTATCTATT  
 ATATATTAAC CATTCTGCT GCTGCGCTGC AAAGCCATAG CAGATTGAG GCGCTGTTGA GGACTGAATT  
 ACTCTCCAAG TTGAGAGATG TCTTGGGTT AAATTAAAAG CCCTACCTAA AACTGAGGTG GGGATGGGA  
 15           GAGCCTTGC CTCCACCATT CCCACCCACC CTCCCTTAA ACCCTCTGCC TTGAAAGTA GATCATGTTC  
 ACTGCAATGC TGGACACTAC AGGTATCTGT CCCTGGGCCA GCAGGGACCT CTGAAGCCTT CTTGTGGCC  
 TTTTTTTTTT TTCATCCTGT GGTTTTCTA ATGGACTTTC AGGAATTTC TAATCTCATA ACTTTCCAAG  
 CTCCACCACT TCCTAAATCT TAAGAACTTT AATTGACAGT TTCAATTGAA GGTGCTGTT GTAGACTTAA  
 CACCCAGTGA AAGCCCAGCC ATCATGACAA ATCCTTGAAT GTTCTCTAA GAAAATGATG CTGGTCATCG  
 CAGCTTCAGC ATCTCCTGTT TTTGATGCT TGGCTCCCTC TGCTGATCTC AGTTTCTGG CTTTCCCTC  
 20           CTCAGCCCC TCTCACCCCT TTGCTGTCC GTGTAGTGTAT TTGGTGAGAA ATCGTTGCTG CACCCCTCC  
 CCAGCACCAT TTATGAGTCT CAAGTTTAT TATTGCAATA AAAGTGCTT ATGCCGAAT TC-3' (FRAG.NO:\_)  
 (SEQ. ID NO:2497)  
 5' GCGCCGCCA TGGGAGTGCA GGTGGAAACC ATCTCCCCAG GAGACGGGCG CACCTCCCC AAGCGGGCC  
 AGACCTGCGT GGTGCACTAC ACCGGGATGC TTGAAGATGG AAAGAAATT GATTCCTCCC GGGACAGAAA  
 CAAGCCCTT AAGTTTATGC TAGGCAAGCA GGAGGTGATC CGAGGCTGGG AAGAAGGGGT TGCCCAGATG  
 AGTGTGGTC AGAGAGCCAA ACTGACTATA TCTCCAGATT ATGCCTATGG TGCCACTGGG CACCCAGGCA  
 TCATCCCACC ACATGCCACT CTCGTCTTCG ATGTGGAGCT TCTAAAATG GAATGACAGG AATGGCCTCC  
 TCCCTTAGCT CCCTGTTCTT GGATCTGCCR TGGAGGGATC TGGTGCCTCC AGACATGTGC ACATGARTCC  
 ATATGGAGCT TTCCACTCCA CTTTGTATAG ACATCTGCC TGACTGAATG TGTTCTGTCA  
 CTCAGCTTGT CTTCCGACAC CTCTGTTCC TCTTCCCTT TCTCCTCGTA TGTGTGTTA CCTAAACTAT  
 ATGCCATAAA CCTCAAGTTA TTCA-3' (FRAG. NO:\_) (SEQ. ID NO:2498)

25           wherein B is adenine, or, more preferably, replaces adenine and is an "equivalent" or a "universal" base, and adenine A<sub>2a</sub> receptor agonist or only minimally antagonist, an adenine A<sub>2b</sub> receptor antagonist, an adenine A<sub>3</sub> receptor antagonist, or an adenine A<sub>1</sub> receptor antagonist. Similarly, adenine (A) may always be replaced by an "alternative", "equivalent" and/or "universal" base having a small fraction, preferably less than 0.3 of the activity of adenine at the adenine receptor(s), as described above.

30           In one preferred embodiment, the links between neighboring mononucleotides are phosphodiester links. In another preferred, at least one mononucleotide phosphodiester residue of the anti-sense oligonucleotide(s) is substituted by a methylphosphonate, phosphotriester, phosphorothioate, phosphorodithioate, boranophosphate, formacetal, thioformacetal, thioether, carbonate, carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxide, sulfide, hydroxylamine, 2'-O-methyl, methylene(methyimino), methyleneoxy (methylimino), phosphoramidate residues, and combinations thereof. The oligos having one or more phosphodiester residues substituted by one or more of the other residues are generally longer lasting, given that these residues are more resistant to hydrolysis than the phosphodiester residue. In some cases up to about 10%, about 30%, about 50%, about 75%, and even all phosphodiester residues may be substituted (100%). Typically, the multiple target anti-sense oligonucleotide (oligo) of the invention comprises at least about 7 mononucleotides, in some instances up to 60 and more mononucleotides, preferably about 10 to about 36, and more preferably about 12 to about 21 mononucleotides. However, other lengths are also suitable depending on the length of the target macromolecule. Examples of the MTA oligos of the invention are provided in Table 3 below, which includes ninety-four sequences (SEQ ID NOS.: 2316 through 2410).

Table 3: MTA Oligos, Location Targeted &amp; Target

45	MTA Oligo	SEQ. ID No.	Location	Compound Targeted	Target
<b>HUMNFKBP65A AS</b>					
	CCC GGC CCC GCC TCG TGC C	3019	5'=1	EPI 2192	
	CGT CCB TGC CGC GGG CCC	3020	5'=28 (AUG)	EPI 2193	
50	GCC CCG CTG CTT GGG CTG CTC TGC CGG G	3021	5'=65	EPI 2194	
	TCT GTG CTC CTC TCG CCT GGG	3022	5'=137	EPI 2195	
	TGG TGG GGT GGG TCT TGG TGG	3023	5'=159	EPI 2196	
	CTG TCC CTG GTC CTG TG	3024	5'=196	EPI 2197	
	GGT CCC GCT TCT TC	3025	5'=362	EPI 2198	
	GGG GTT GTT GTT GGT CTG G	3026	5'=401	EPI 2199	
55	TGT CCT CTT TCT GC	3027 [3026]	5'=656	EPI 2200	
	GCC TCG GGC CTC CC	3028 [3027]	5'=697	EPI 2201	
	GGC TGG GGT CTG CGT	3029 [3028]	5'=769	EPI 2202	

5	GGC CGG GGG TCG GTG GGT CCG CTG GGG CTG GGG TGC TGG CTT GGG G GGG GCT GGG GCC TGG GCC GCC TGG GTG GGC TTG GGG GC GCT GGG TCT GTG CTG TTG CC GTT GTG TGG GGG GCC GCT GGG TCG GGG GGC CTC TGG GCT GTC GCC CCG GGG CCC CC TGG CTC CCC CCT CC GCT CCC CCC TTT CC CGG ACG AAG ACA GAG A GGC TTT GTG GGC TC GCC TGC TCT CCC CC CCC GGC CCC GCC BCG BBC C CCC GGC CCC GCC BCG BBC C CCC GGC CCC GCC BCG BBC C CCC GBC CCC GCC TCB BG CCC GBC CCC GCC TC 20	3030 [3029] 5'=953 3031 [3030] 5'=1022 3032 [3031] 5'=1208 3033 [3032] 5'=1272 3034 [3033] 5'=1362 3035 [3034] 5'= 1451 3036 [3035] 5'=1511 3037 [3036] 5'=1550 3038 [3037] 5'=1772 3039 [3038] 5'=1863 3040 [3039] 5'=1979 3041 [3040] 5'=2011 3042 [3041] 5'=2312 3043 [3042] intron 3044 [3043] intron 3045 [3044] 5'untr 3046 [3045] 5'untr 3047 [3046] trans 3048 [3047] trans 3049 [3048] 5'untr 3050 [3049] 5'trans 3051 [3050] 5'untr 3052 [3051] 3'trans 3053 [3052] intron 3054 [3053] intron 3055 [3054] 5'trans 3056 [3055] 3'trans 3057 [3056] 5'untrs 3058 [3057] 5'untrs 3059 [3058] 5'UTR 3060 [3059] 3'UTR 3061 [3060]	EPI 2203 EPI 2204 EPI 2205 EPI 2206 EPI 2207 EPI 2208 EPI 2209 EPI 2210 EPI 2211 EPI 2212 EPI 2213 EPI 2214 EPI 2215 EPI 2192-01A HSU50136C4Synth EPI 2192-01B EPI 2192-02A HUMLIPOX5LO EPI 2192-02B EPI 2192-03A HSNFKBS Subunit EPI 2192-03B EPI 2192-04 TGF $\beta$ R1 EPI 2192-05A HSU58198I1 enhan EPI 2192-05B EPI 2192-06 HSVECAD EPI 2192-07A NFKB2 EPI 2192-07B NFKB2 EPI 2192-08 Carboxypep EPI 2192-09 HumADRA2Ca2AdrKid EPI 2192-10 HUMFK506B EPI 2192-11 HSNBARKS1 $\beta$ AdrKin EPI 2192-12 HSNFXN1 (NFKB1) EPI 2192-13 HSILF(transcrp. Factor ILF) EPI-2192-14 NFKB/C4Syn/5-LO/ TGF $\beta$ rec1 MTA EPI-2192-15NFKB/C4Syn/5-LOMTA EPI-2193-01 METOncogene EPI-2193-02 HSFGR2 (IG) EPI-2193-03 5-LO EPI-2193-04 HUMTK14 EPI-2193-05 HUMTNFR Probl. HUMPTCH cardiacK+channel humCSPAcytotox. Ser. Protease EPI-2195-01 HSINOSX08induc.NOS EPI-2195-02 HUMACHRM2musc.m2 acetylch.rec. EPI-2195-04 s86371s1 Neurokinin3Recept EPI-2195-05 HUMMIP1 Amacro
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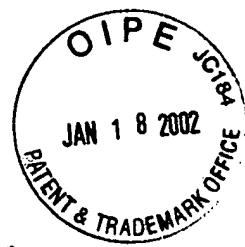
Table 3: MTA Oligos, Location Targeted &amp; Target (Cont'd)

MTA Oligo	SEQ. ID No.	Location	Compound Targeted	Target
5 CTC CTC TBG CCT GG	3074 [3073]		EPI-2195-06	HSNBARKS4
5 GTG CTC CBB TCB BCT GGG	3075 [3074]		EPI-2195-07	$\beta$ -Adr Rec Kinase
5 GTG CBC CBB TCB CCT GGG	3076 [3075]		EPI-2195-08	HSTMFR2SO6TNF R2 humfkbp fk506 binding prot.
10 TCT GTG CBC CTC TBG BCT	3077 [3076]	exon	EPI-2195-09	HSNBARKS1 $\beta$ -Adr. Recept.Kinase
10 CTG TBB TCC TBB CBC CTG G	3078 [3077]		EPI-2195-10	HUMIL8
10 TGT GCT BBT CBC BCB TGG G	3079 [3078]		EPI-2195-11	HSU50157 PDE4
10 GTG CBC CBC TCB CCT G	3080 [3079]	intron/exon	EPI-2195-12	IL-2 R
10 CTG TGC BCC TCT C	3081 [3080]		EPI-2203-05	IL-6 R HSIL6R
15 CBG TGC BCC BCT CBC CTG	3082 [3081]	intr/ex	EPI-2203-06A	HSIL2rG6
15 G TGC BCC BCT CBC CTG	3083 [3082]		EPI-2203-06B	HSIL2rG6
15 CBC CTC TCB CCT GGG	3084 [3083]	coding	EPI-2203-07A	HUMIL71
15 C CTC TCB CCT GGG	3085 [3084]		EPI-2203-07B	IL-7 HUMIL71
20 GCT CCB CTC GCC T	3086 [3085]	coding	EPI-2203-08	IL-6 R HSI6REC
20 TGC TCC TCB CGC C	3087 [3086]		EPI-2303-09	Chain HUMPDGFAB
20 GTT GTT GBT CTG G	3088 [3087]	3'utr	EPI-2199-01	GATA-4Transcrip. Factor for IL-5
25 GGT TGB BBT TGG TCT TGG	3089 [3088]	Coding	EPI-2199-02	TNF $\alpha$ HUMTNFA
25 GGT TGT TGB TGB TCT G	3090 [3089]		EPI-2199-03	HSSUBP1G(Sub Pr)
25 GGG TTG BBG TTG BTC TGG	3091 [3090]	Coding	EPI-2199-04	NeutrophilAdh. R HUMNARIA
30 GGG TTG BBG TTG BTC TGG	3092 [3091]		EPI-2199-05	m2 Muscarinic R
30 TTG TTG TGB BTC TGG	3093 [3092]	HSHM2	EPI-2199-06	L1 LeukAadhProt
30 GGG TGB BBG BGT CCG CTG	3094 [3093]		EPI-2203-01	HUMGATA2A
30 GGG TCB GBG GBT CBG CTG	3095 [3094]	S71424S2	EPI-2203-02	IGE eps
30 GGG TBG GTG GGT C	3096 [3095]		EPI-2203-03	HSGCSFR2
30 GGG TCG GBG GGT CBG C	3097 [3096]	HUMITGF	EPI-2203-04	TGF $\beta$ 3
30 GGG TGG GCT T	3098 [3097]		EPI-2206-01	NFKB/NK & TCell
35 GGG TGG GCT TGG G	3099 [3098]	HUMPEREEB	EPI 2206-02	Activating Prot NFKB/Prostagl. EP3 Rec
35 CCTGGGTGGGBTGGG	3100 [3099]		EPI 2206-03	HSNF2B/GCSF NFKB/GranaLocCSF/ Transcr.FactorNF2B
40 CCTGGGBTGGCBTGGG	3101 [3100]		EPI-2206-04	HUMLAP/NFKB
40 GCCTGBTGBBCTTGGG	3102 [3101]		EPI2206-05	Leuk. Adhes. Prot NFKB/Endothel N2 S63833
45 CCCAVGVCCVCCCAGGC	3103 [3102]		EPI 2206-06	NFKBAS13/B Lymph SerThrProt.Kinase
45 AGCCCACCCAGGC	3104 [3103]		EPI2206-07	NFKBAS13/GCSF1 HSGCSFR1Rec
50 BCCTGGGTGGGCTB	3105 [3104]		EPI2206-08	NFKBAS13/GCSF1/ NK7TCELLACT.Prot
50 GGTGGGCTTGGG	3106 [3105]		EPI 2206-09	NFKBAS13/ HSTGFB1 TGFB
50 CCBBGGTGGGCTTGGG	3107 [3106]		EPI 2206-10	NFKBAS13/ HSTGFB1 TGFB1
55 CTGGGTGGGBTGGG	3108 [3107]		EPI 2206-11	NFKBAS13/ HSGCSFR1 GCSFR1
55 CCBGGGTGGGCTTGG	3109 [3108]		EPI 2206-12	NFKBAS13/HUMCD30A LymphActAntigCoding
60 GGGTGGGCTTGG	3110 [3109]		EPI-2206-12B	NFKBAS13/HUMCD30A
60 CCTGBTGBGCBTGGG	3111 [3110]		EPI 2206-13	NFKBAS13/HUMCAM1V Vasc. Endoth. Cell Adh. Molec

B: Universal Base

The MTA oligos of Table 3 are suitable for use with two or more of the targets listed in Table 4 below.

**CLEAN VERSION**



**In the specification**

Please enter the following pages 296 through 298 for the substitution of the previous original pages (starting from next page):